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June 16, 2000

Ms. Jane Axelrad, J.D.
Associate Director of Policy
Center for Drugs Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Regarding: Docket 00D-0892; FR March 10, 2000

Dear Ms. Axelrad:

We appreciated the opportunity to have an open discussion with you and the FDA staff about the proposed guidance on the content and format of new drug applications for PET radiopharmaceuticals. Outlined below are the PET Radiopharmaceutical Committee's written comments addressing its major concerns with respect to the draft documents published by the FDA in the Federal Register (March 10, 2,000) and additional issues addressed at the meeting of March 22nd, 2000. We also refer you to the public documentation of this meeting for additional comments and concerns of the committee.

General Comments:

The committee was pleased with the work performed by your staff to facilitate compliance with proposed FDA regulations for PET radiopharmaceuticals. This intense effort toward the established goal of a meaningful approach to the regulation of PET radiopharmaceuticals has already resulted in a much-simplified method that will permit the integration of PET into clinical care. Further, it is our hope that this new process will facilitate the introduction of the PET technology into drug development for the benefit of the public at large. Nevertheless, we did, however, identify some areas in the guidance (and templates) that will benefit from further thought and analysis. Our comments are detailed below.

(i) The committee remains concerned about the title and the references in the document as to this being guidance for "industry" and drug manufacturers. While we understand why the Agency chose to issue the document as such, we feel that maintaining that focus is wrong, unless the intent is to make this guidance applicable to industry with exclusion of academic centers and hospitals. Since this doesn't appear to be the case, the wording in the guidance has produced concern and consternation within the community. Without knowing specifically the options available to the Agency, we would recommend that the guidance be issued for industry, with appropriate exceptions made for academic institutions and hospitals

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(ii) On a related issue, the committee was also gravely concerned about the exclusion of reference in the guidance distinguishing differences between academic/non-profit facilities with industry/for-profit facilities. This distinction is mandated by FDAMA 97 to minimize the regulatory burden imposed by FDA oversight to academic institutions/hospitals. We hope that this will be addressed in this guidance and the one that will be issued relating to manufacturing practices.

(iii) Also notably absent in this guidance is a reference to the need to register as drug establishments with the FDA for submission of NDAs and/or ANDAs. Through our discussions, we understand that the Agency intends for all sites to register. As you know, the community strongly opposes this initiative for sites whose primary mission is patient care. We believe that an alternative to the registration process should be developed for non-commercial PET production sites.

(iv) In addition, it has remained unclear to many whether off-label use of these drugs will still be allowed. The concern was raised because a physician that may be the sponsor of the NDA may also be prescribing the drug for an off-label use. Along the same lines, if the Institution were a sponsor of the NDA, how would the practice of medicine of its physician-employees be altered when prescribing the PET drugs or when giving lectures and/or educational symposia for off-label uses? These are critical practical issues that must be addressed to avoid a collision course with the practice of medicine at sites that produce their own PET radiopharmaceuticals. We strongly believe that the practice of medicine must be preserved and would like to see the clarification of this in the guidance.

(v) In regards to exclusivity of use and the waiver of fees, we commend the Agency for implementing a creative mechanism to ensure that these publicly sponsored safety and efficacy evaluations are available to the community at large. The recent approval of the Peoria NDA supplement guarantees this for the new FDG indications. Fundamentally, however, we feel that a mechanism should be developed within FDA to guarantee that exclusivity is waived on publicly sponsored initiatives such as this one. On the other hand, as commercial entities begin to produce their own safety and efficacy evaluations for unique radiopharmaceuticals that they develop, exclusivity will be an important incentive to their introduction. In this case, we believe that exclusivity should not have to be waived in order for the entity to receive a fee waiver for which they may otherwise be entitled to (i.e., small company).

(vi) We would recommend that the Agency define marketing as it is meant in this guidance. The community and the Agency's definition is likely quite different.

(vii) We would also like to reiterate to the Agency that we feel it is imperative to resolve other issues pertaining to PET radiopharmaceuticals, particularly as they relate to the IND and RDRC processes, before finalizing the regulation of PET drugs. The scope of this extends from appropriateness of toxicology assessments to clinical trial design.

(viii) We would also like to note that cGMPs for PET radiopharmaceuticals are under development and were not a specific topic of this meeting. However, the nature of such cGMPs and the associated amount of documentation and validations required remain of significant concern to the PET community. As stated at the meeting, we encourage that the cGMPs for PET be performance-based, focusing on the acceptability of the final product/batch. Likewise, the inspection of PET facilities for compliance with these PET cGMPs should be performance-based.

(ix) We would like to reiterate the desire of the Committee to have ongoing input into the implementation of cGMPs, as NDAs are filed and inspections take place. We believe that the ongoing input of the Committee into the interpretation of cGMPs is essential to the success of this entire effort.

(x) Finally, the Committee was very pleased with the safety and efficacy evaluations of FDG, NH3, and F- conducted by the FDA and published at the same time. For the other radiopharmaceuticals under consideration, we look forward to continuing the positive interchange and learning how to conduct the evaluation of other radiopharmaceuticals in the future.

Specific Comments about the CMC and labeling components:

Current model CMC submission: The committee is concerned that the documentation and validation requirements outlined in the current model CMC submission (i.e., to be submitted to address compliance with the USP Chapter on the Compounding of PET Radiopharmaceuticals) substantially exceeds the documentation and validation requirements intended by the USP Chapter. I.e., the submission requirements outlined in this model CMC submission appear to be more consistent with cGMP requirements. It is recommended that the FDA develop a **full, complete** model NDA application based on the this current model to allow the community to fully understand the level of detail and validation that is required.

Isotonicity of FDG: Attachment 1, p. 25 states that FDG needs to be isotonic. We request that this reference be removed. As per current USP guidelines, FDG does not need to be isotonic.

Radiochemical Purity of FDG: We request that the requirement for a no greater than 4% fluoride ion impurity be removed. This is inconsistent with the USP and inconsequential to the quality of the drug product. We understand that this restriction was determined because of the "clinical" dose set forth in the prior fluoride ion NDA, issued by the Agency in the 70s. As discussed at the meeting, the dosage level was originally set based on equipment limitations, not for clinical reasons.

Microbiological Sections in CMC: Why is there a reference to CFR 211 in the microbiological sections of the CMCs? Will the PET cGMPs be in CFR 211?

Kryptofix Specifications: There is a typographical error on page 25 of Attachment I in the specifications for Kryptofix. Current document states limits of 50 g.

Critical Components and Acceptance Tests We believe, as stated during the discussions, that manufacturer specifications and quality control determinations should suffice as acceptance criteria for all critical components. In the absence of these specifications, the applicant should perform logical appropriate tests.

F-18 Fluoride and FDG labeling: We recommend that the pediatric dosing schedule reflect a range based upon patient weight. Furthermore, administration of FDG should be done while the patient is at rest, so as to minimize muscle uptake of FDG. And finally, the dose for F-18 fluoride using the current generation of imaging equipment should be 10 mCi, based upon current literature.

In closing, once again, we thank the FDA for all their efforts towards a constructive approach for defining new PET radiopharmaceutical regulations. We believe that these new regulations will be an important milestone upon which the future of PET in clinical practice, biological research and drug development will be built.

Respectfully,

Jorge Barrio /jc

Jorge R. Barrio, Ph.D.
Chairman
Radiopharmaceutical Committee

c. PET Docket

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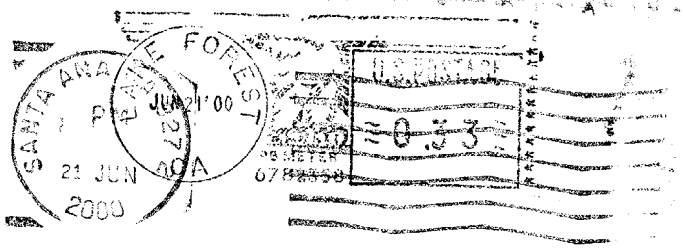

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